Texas Vendor Drug Program

Drug Use Criteria: Anti-Depressants, Selective Serotonin Reuptake Inhibitors

Publication History

1. Developed: March 2017
2. Revised **April 2023**; April 2021; March 2019

Medications listed in the tables and non-FDA approved indications that may be included in these retrospective criteria are not indicative of Vendor Drug Program formulary coverage.

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1 Dosage

1.1 Adults

The FDA requires that all antidepressant drugs display a black box warning describing the potential for increased suicidal thinking and behavior **compared to placebo** when prescribed to young adults (18 to 24 years of age) with MDD and other psychiatric disorders. In short-term clinical trials, the suicide risk was increased in young adults managed with antidepressants compared to those receiving placebo in the first few months of treatment. Suicide risk was not shown to increase in adults over 24 years of age, and patients 65 years of age and older manifested a decreased suicide risk. **Patients of all ages** prescribed antidepressant drugs should be closely monitored for changes in behavior, **clinical worsening, or suicidality**.[1-2]

Citalopram is FDA approved for treatment of major depressive disorder (MDD), escitalopram is FDA approved for generalized anxiety disorder (GAD) and MDD. Fluoxetine is FDA approved for bipolar I disorder (BD), bulimia nervosa (BN), obsessive compulsive disorder (OCD), panic disorder (PD), premenstrual dysphoric disorder (PMDD), and MDD. Fluvoxamine is FDA approved for OCD. Paroxetine is FDA approved for seasonal affective disorder (SAD), post-traumatic stress disorder (PTSD), vasomotor symptoms associated with menopause (VMS), GAD, MDD, OCD, PDD, and PMDD. Sertraline is FDA approved for MDD, OCD, PD, SAD, PTSD, and PMDD. Olanzapine/Fluoxetine is FDA approved for treatment resistant depression (TRD) and BD.[1-17]

Maximum recommended daily doses for SSRI antidepressant drugs in adults, including the elderly population, are summarized in Tables 1 and 2 for both monotherapy and SSRI combination therapy, respectively. However, in all patients, the lowest effective antidepressant dose should be utilized to minimize unwanted adverse effects. Patient profiles with SSRI antidepressant dosages exceeding these recommendations will be reviewed.

Table 1. Oral SSRI Medications - Adult Maximum Recommended Dosages – Monotherapy[3-17]

Drug Name	Available Dosage Strengths	Treatment Indication	Maximum Recommended Dosage	
			≤ 65 years	*> 65 years*
citalopram (Celexa®, generics)	10 mg, 20 mg, 40 mg tablets; **30 mg capsule;** 10 mg/ 5 mL oral solution	MDD	40 mg/day	20 mg/day (older than 60 years)
escitalopram (Lexapro®, generics)	5 mg, 10 mg, 20 mg tablets; 5 mg/5 mL oral solution	GAD, MDD	20 mg/day	10 mg/day
fluoxetine (Prozac®, generics)	10 mg, 20 mg, 40, mg capsules; 10 mg, 20 mg, 60 mg tablets; 20 mg/5 mL solution	MDD, OCD	80 mg/day	80 mg/day
		BN, PD	**60 mg/day**	**60 mg/day**
		BD, TRD	**75 mg/day^**	**75 mg/day^**
fluoxetine (Prozac® Weekly, generics)	90 mg delayed-release capsules	MDD	90 mg/week	90 mg/week
fluoxetine (Prozac Pulvules®)	10 mg, 20 mg, 40 mg pulvules	**MDD, OCD**	**80mg/ day**	**80 mg/ day**
		BN, PD	**60 mg/day**	**60 mg/day**

Drug Name	Available Dosage Strengths	Treatment Indication	Maximum Recommended Dosage	
		BD, TRD	**75 mg/day^**	**75 mg/day^**
fluoxetine (generics)	10 mg, 20 mg capsules	PMDD	80 mg/day	---
fluvoxamine (generics)	IR: 25 mg, 50 mg, 100 mg tablets ER: 100 mg, 150 mg 24-hour capsules	OCD	300 mg/day*	300 mg/day*
paroxetine mesylate (Pexeva®)	10 mg, 20 mg, 30 mg, tablets	GAD, MDD	50 mg/day	40 mg/day
		OCD, PD	60 mg/day++	40 mg/day
paroxetine HCl (Paxil®, generics)	10 mg, 20 mg, 30 mg, 40 mg tablets, 10 mg/ 5 mL suspension	OCD, PD	60 mg/day	40 mg/day
		MDD, PTSD	50 mg/day	40 mg/day
		SAD	**60 mg/day++**	**40 mg/day**
		GAD	**50 mg/day++**	**40 mg/day**
paroxetine HCl (Paxil CR®, generics)	12.5 mg, 25 mg, 37.5 mg 24-hour ER tablets	MDD	62.5 mg/day	50 mg/day
		PD	75 mg/day	50 mg/day
		SAD	37.5 mg/day	**37.5 mg/day**
		PMDD	25 mg/day	---
Paroxetine mesylate (Brisdelle®, generics)	7.5 mg capsule	VMS	7.5 mg/day at bedtime	7.5 mg/day at bedtime

Drug Name	Available Dosage Strengths	Treatment Indication	Maximum Recommended Dosage	
sertraline (Zoloft®, generics)	25 mg, 50 mg, 100 mg tablets; 20 mg/mL oral concentrate	MDD, OCD, PD, SAD, PTSD	200 mg/day	200 mg/day[+]
			150 mg/day	---

BD = bipolar I disorder; BN = bulimia nervosa; CR = controlled-release; ER = extended-release; GAD = generalized anxiety disorder; IR = immediate-release; MDD = major depressive disorder; OCD = obsessive-compulsive disorder; PD = panic disorder; PMDD = premenstrual dysphoric disorder; PTSD = posttraumatic stress disorder; SAD = social anxiety disorder; TRD = treatment-resistant depression; VMS = vasomotor symptoms associated with menopause
*[*]Fluvoxamine IR doses > 100 mg daily should be administered in divided doses**, if dose is unequal larger doses should be given at bedtime***
[++]Data do not confirm that paroxetine doses greater than 20 mg/day are more effective
[+]Lower doses may be required in elderly patients
[^]In combination with olanzapine

Table 2. Oral SSRI Medications - Adult Maximum Recommended Dosages – Combination Therapy[1-2, 17]

Drug Name	Available Dosage Strengths	Treatment Indication	Maximum Recommended Dosage	
			≤ 6 years	*> 65 years*
olanzapine/ fluoxetine (Symbyax® , generics)	3 mg/ 25 mg, 6 mg/ 25 mg, 12 mg/25 mg, 6 mg/ 50 mg, 12 mg/ 50 mg capsules	BD, TRD	18 mg/ 75 mg per day	18 mg/ 75 mg per day

BD = bipolar I disorder; TRD = treatment-resistant depression

Pediatrics

The FDA requires that all antidepressant drugs display a black box warning describing the potential for increased suicidal thinking and behavior when prescribed to children and adolescents with MDD and other psychiatric disorders. In short-term clinical trials, the suicide risk occurred twice as frequently with antidepressant-treated children/adolescents compared to those receiving placebo (4% vs. 2%, respectively) in the first few months of treatment. Pediatric patients prescribed antidepressant drugs should be closely monitored for changes in behavior.[1-2]

Citalopram and paroxetine are not FDA-approved for use in pediatric patients as safety and effectiveness in this age group have not been well established.[3, 11-14] The olanzapine/fluoxetine combination is FDA-approved in pediatric patients.[17]

Maximum pediatric recommended doses for SSRI antidepressants approved for use as monotherapy and combination therapy are summarized in Tables 3 and 4, respectively. An additional column reflecting literature-based dosing included in the Texas Health and Human Services Psychotropic Medication Utilization Parameters for Children and Youth in Texas Public Behavioral Health (6th Version) is included in Tables 3 and 4. Dosages exceeding these recommendations will be reviewed.[18]

Table 3. Recommended SSRI Antidepressant Drug Dosages for Pediatric Patients – Monotherapy[1-18]

Drug Name	Available Dosage Strengths	Treatment Indication	Literature Based Maximum Dosage	FDA Approved Maximum Recommended Dosage
citalopram (Celexa®)	10 mg, 20 mg, 40 mg tablets; **30 mg capsule;** 10 mg/ 5 mL oral solution	MDD	*≥6 years of age:* 40 mg/ day	*Not FDA approved for children & adolescents*
escitalopram (Lexapro®, generics)	5 mg, 10 mg, 20 mg tablets; 5 mg/5 mL oral solution	MDD	*6-11 years of age*: 20 mg/ day *≥12 years of age:* 30 mg/day	*12 to 17 years of age:* 20 mg/day
fluoxetine (Prozac®, generics)	10 mg, 20 mg, 40 mg capsules; 10 mg, 20 mg, 60 mg tablets; 20 mg/5 mL solution	MDD	*≥6 years of age: 6*0 mg/ day	*8 to 18 years of age:* 20 mg/day
		OCD	*≥6 years of age: 6*0 mg/ day	*7 to 17 years of age:* • lower weight children: 30 mg/day • higher weight children: 60 mg/day
Fluoxetine (Prozac Pulvules®)	10 mg, 20 mg, 40 mg pulvules	BD		10 to 17 years of age: 50 mg/ day^
		MDD	**8 to 18 years of age: 20 mg/day**	**8 to 18 years: 20 mg/day**

Drug Name	Available Dosage Strengths	Treatment Indication	Literature Based Maximum Dosage	FDA Approved Maximum Recommended Dosage
		OCD	**7 to 17 years of age: 60 mg/day**	**7 to 17 years: 60 mg/day**
fluvoxamine (generics)	IR: 25 mg, 50 mg, 100 mg tablets	OCD	*Age 8-11 years:* 200 mg/day *Age 12-17 years:* 300 mg/day	*8-11 years of age:* 200 mg/day[#] *12 to 17 years of age:* 300 mg/day[#]
Fluvoxamine controlled release (Luvox CR®, generics)	CR: 100 mg, 150 mg **capsules**	OCD	*Age 8-11 years:* 200 mg/day *Age 12-17 years:* 300 mg/day	*8-11 years of age:* 200 mg/day *12 to 17 years of age:* 300 mg/day
sertraline (Zoloft®, generics)	25 mg, 50 mg, 100 mg tablets; 20 mg/mL oral concentrate	OCD	*Age ≥ 6 years:* 200 mg/day	*6 to 17 years of age:* 200 mg/day

BD = bipolar I disorder; IR = immediate-release; MDD = major depressive disorder; OCD = obsessive-compulsive disorder
*[#]Fluvoxamine IR doses > 50 mg daily should be administered in divided doses, **if the two doses are unequal the larger dose should be given at bedtime***
^In combination with olanzapine

Table 4. Recommended SSRI Antidepressant Drug Dosages for Pediatric Patients –Combination Therapy[1-2, 17-18]

Drug Name	Available Dosage Strengths	Treatment Indication	Literature Based Maximum Dosage	FDA Approved Maximum Recommended Dosage
olanzapine/ fluoxetine (Symbyax®, generics)	3 mg/ 25 mg, 6 mg/ 25 mg, 12 mg/25 mg, 6 mg/ 50 mg, 12 mg/ 50 mg capsules	BD	*Age 10-17 years:* 12 mg olanzapine/50 mg fluoxetine once daily	*10 to 17 years of age:* 12 mg/50 mg per day

BD = bipolar I disorder

Renal Impairment

Many antidepressants do not require significant dosage modifications in renal impairment. However, dosage guidelines for select SSRIs in renal impairment are

available. Table 5 summarizes dosage modifications and/or restrictions for specific SSRI antidepressant medications.

Table 5. Select SSRI Antidepressant Dosage Modifications in Renal Impairment[1-5, 12-13]

Drug Name	Dosage in Renal Impairment
Citalopram	Severe renal impairment (creatinine clearance < 20 mL/min): use cautiously, as specific dosage guidelines not available
Escitalopram	Severe renal impairment (creatinine clearance < 20 mL/min): use cautiously, as specific dosage guidelines not available
Paroxetine (Paxil®, Pexeva®, Paxil CR®)	Serum levels, AUC increase as renal function declines; therefore, maximum doses when creatinine clearance < 30 mL/min are: • IR: 40 mg/day • CR: 50 mg/day

CR = controlled-release; IR = immediate-release

2 Duration of Therapy

There is no basis for limiting antidepressant therapy duration when used to manage MDD, OCD, GAD, PTSD, or PD as these disorders can all be characterized as chronic conditions.

Clinical trials have documented fluoxetine efficacy in BN management for up to 52 weeks. Fluoxetine has demonstrated efficacy in PMDD for up to 6 months when administered continuously and up to 3 months when administered intermittently.[6-9] Paroxetine and sertraline have demonstrated efficacy in PMDD for up to 6 months and 12 months, respectively, in clinical trials.[11-14, 16] Patients should be assessed periodically to determine need for continued treatment. However, the potential exists for PMDD symptoms to worsen with advancing age until patients reach menopause. Patients responding to fluoxetine, paroxetine, or sertraline therapy for PMDD may benefit from chronic administration.[6-9, 11-14, 16]

Paroxetine treatment for VMS exceeding 24 weeks has not been evaluated in clinical trials. Additionally, paroxetine dosages used to manage VMS are not FDA-approved to manage psychiatric conditions, as the dose contained in Brisdelle® is lower than the recommended doses used to manage psychiatric disorders. Patients requiring paroxetine for psychiatric disorders should discontinue Brisdelle® and initiate therapy with a paroxetine formulation FDA-approved for psychiatric use.[14]

3 Duplicative Therapy

The concurrent use of two SSRI antidepressant medications with the same spectrum of activity may not be justified and will be reviewed.

4 Drug-Drug Interactions

Patient profiles will be assessed to identify those drug regimens which may result in clinically significant drug-drug interactions. The following drug-drug interactions summarized in Table 6 are considered clinically relevant for SSRI antidepressants. Only those drug-drug interactions identified as clinical significance level 1 or those considered life-threatening which have not yet been classified will be reviewed.

Table 6. Major Drug-Drug Interactions for SSRI Antidepressant Drugs[1, 3-17]

Target Drug	Interacting Drug	Interaction	Recommendation	Clinical Significance Level[#]
fluoxetine	ergot derivatives	increased risk of ergotism due to fluoxetine inhibition of CYP3A4-mediated ergot metabolism	avoid concurrent use	**moderate** (CP)
SSRIs	anticoagulants	co-administration may increase bleeding risk due to impaired platelet aggregation most likely resulting from platelet serotonin depletion	patients should be monitored for signs/symptoms of bleeding (including INR) if combined therapy necessary	moderate (CP)
SSRIs	drugs with serotonergic properties (e.g., antipsychotics, tramadol, triptans) or dopamine antagonist properties (e.g., phenothiazines, metoclopramide)	combined use may increase risk of serotonin syndrome or neuroleptic malignant syndrome (NMS)	cautiously administer concurrently and closely observe for signs/symptoms of serotonin syndrome or NMS, especially with treatment initiation or dosage increases	**Moderate (CP)**

Target Drug	Interacting Drug	Interaction	Recommendation	Clinical Significance Level[#]
SSRIs	MAOIs	increased risk of serotonin syndrome (e.g., mental status changes, hyperpyrexia, **autonomic instability, neuromuscular symptoms, seizures and/or gastrointestinal symptoms,** restless, shivering, hypertonia, tremor) due to serotonin metabolism inhibition by monoamine oxidase	allow 14 days after MAOI discontinuation before initiating other antidepressant therapy; wait 5 weeks after discontinuing fluoxetine before initiating MAOIs	**contraindicated** (CP)
SSRIs	tramadol	increased risk of serotonin syndrome and seizures due to increased nervous system serotonin concentrations (additive effects on serotonin, SSRI inhibition of CYP2D6-mediated tramadol metabolism) as well as potential reduced seizure threshold with SNRIs, SSRIs	avoid concurrent use	**moderate** (CP)
SSRIs	pimozide	increased risk of pimozide toxicity including cardiotoxicity (QT prolongation) due to elevated plasma concentrations or additive effects on QT interval	avoid concurrent used	severe (CP)
SSRIs	select phenothiazines (thioridazine)	increased risk of somnolence, bradycardia and serious cardiotoxicity (QT prolongation, torsades de pointes) due to potential additive effects on QT	avoid concurrent use; if adjunctive use necessary, monitor for increased pharmacologic/toxic effects; adjust dose as necessary	**contraindicated** (CP)

Target Drug	Interacting Drug	Interaction	Recommendation	Clinical Significance Level[#]
Citalopram, Escitalopram,	**Chlorpromazine**	**Increased risk of QT prolongation and torsade's de pointes. SSRIs may increase serum concentration of chlorpromazine leading to phenothiazine related reactions. Increased risk for serotonin syndrome.**	**Avoid concurrent use. If adjunctive use is necessary, ECG monitoring is recommended. Monitor for increased pharmacologic/toxic effects; adjust dose as necessary**	**Major (CP)**
SSRI	**Chlorpromazine**	**Increased risk of QT prolongation and torsade's de pointes. SSRIs may increase serum concentration of chlorpromazine leading to phenothiazine related reactions. Increased risk for serotonin syndrome.**	**Should be avoided if possible. If adjunctive use is necessary, ECG monitoring is recommended. Monitor for increased pharmacologic/toxic effects; adjust dose as necessary**	**Major (CP)**

MAOI = monoamine oxidase inhibitor; SNRI = serotonin-norepinephrine reuptake inhibitor; SSRI= selective serotonin reuptake inhibitor
[#]CP = Clinical Pharmacology

5 References

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